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Conference Abstract

Use of biomarkers in CRPC and future treatment in Asia☆

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The importance of biomarkers in prostate cancer medicine is increasing as they are now commonly used as companion diagnostics for prediction and prognostication of response and survival parameters. In terms of screening, they can be important for early diagnosis and prognosis for late diagnosis, and used for monitoring. They can be derived from tissue sources such as the primary tumour, metastatic sites such as bone and lymph nodes or as circulating markers found in blood or urine. Most importantly, biomarkers now can comprise DNA, epigenetic modifications of DNA, RNA species, proteins (most commonly), and even a new generation of bio-molecular molecules such as exosomes is emerging. In castrate resistant prostate cancer clinical trials, they can be used to direct precision medicine.

As discussed in my other abstract, there is a range of emerging molecular aberrations defining castrate resistant prostate cancer in terms of prognosis and molecular subtypes enabling matching molecular aberrations to systemic therapies. These biomarkers may be limited by access such as availability and affordability at present but will soon arrive in the clinic. They may direct clinical trial designs whether they be biomarker driven, such as "basket" or "N of 1" studies. However, there are significant regulatory hurdles and cost effective studies that need to accompany these areas before becoming routine in the clinic. Recent post-hoc analyses of clinical trials using novel androgen synthetic inhibitors such as abiraterone acetate in castrate resistant prostate cancer have demonstrated that radiographic progression free survival may be stratified as a functional percentage in PSA decline.[1] Indeed, the longest radiographic progression free survival is associated with a greater than 90% fallen PSA compared to patients with no decline.[2] Biomarkers such as this may be added to prognostic multi-variant models using clinical parameters such as LDH, performance status, presence or absence of liver metastasis, normal or low values of albumin, raised or normal levels of serum alkaline phosphatase or prior to the commencement of androgen deprivation therapy to initiation of abiraterone acetate use.[3] Validation of models such as these across different patient groups from different institutions has enabled reasonable consensus in this approach.[4] Indeed the latest iteration of approaches such as this may be incorporated in internet-enable nomograms which may be used in the clinic in discussion with patients for decision making (https://www.cancer.duke.edu/Nomogram/firstlinechemotherapy.html). Other clinical biomarkers such as PSA doubling time may also be used to assess prognosis after chemotherapy such as docetaxel use for castrate resistant prostate cancer.[5] Using clinical data such as this novel biomarkers may be incorporated such as circulating tumour cells using CLIA/FDA certified immunomagnetic selection technology.[6] Circulating tumour cell counts of less than 5 cells per 7.5 mL are associated with a significantly increased probability of survival compared to 5 or more circulating tumour cells per ml.[7] Indeed combining circulating tumour cell concentration with normal or elevated levels of lactate dehydrogenase is extremely powerful in predicting overall survival.

Newer molecular analyses of castrate resistant prostate cancer are clearly identifying multiple common genetic aberrations such as androgen receptor amplification. This amplification may be seen as one mechanistic function of resistance in response to previous therapy (acquired resistance) and significant trends have been reported in early clinical studies.[8,9] Recent long-range epigenetic remodelling data from Australia [10] has demonstrated activation of aberrant domains such as kallikrein3 (PSA). Other epigenetic changes such as the expression of microRNA, MiR-20a, MiR-21, and MiR-141 may distinguish molecular sub-types as well as stratify according to metastatic potential.[11]

Tremendous excitement has emerged over the last eighteen months with the identification of ligand binding domain splice variants of the androgen receptor, most important of which is the AR-V7 variant which due to its loss of the ligand binding is associated with intrinsic resistance to androgen receptor targeting therapies. Antonorakis *et al* have clearly demonstrated an association between the presence of AR-V7 containing circulating tumour cells and overall survival both for abiraterone and enzalutamide.[6] In an update of this analysis, for patients receiving docetaxel, however, there was no association between the presence or absence of this splice variant and response to treatment.[12] In their final provocative analysis there is a suggestion that if a patient has significant amounts

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of AR-V7 positive circulating tumour cells then taxanes are most likely to be associated with improvement in PSA progression free survival as well as progression free survival but not overall survival.

Conflicts of interest

PM has been a speaker and an Advisory Board member for Astellas, Janssen, Roche, Novartis and Pfizer.

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